REMARKS/ARGUMENTS

Applicants thank the Examiner for the helpful suggestions during the telephone conference of February 19, 2004.

Applicants note with appreciation that the amendments filed on August 8, 2003 have been entered in full.

Claims 2, 9-12, 16, and 20-25 constitute the pending claims in this application. Claims 3-8 and 17-19 have been canceled without prejudice and Applicants reserve the right to reintroduce these or similar claims in this or future patent applications. Claims 2, 9-12, and 16 have been amended. Support for the amendments of independent claims 2 and 16 may be found, for example, in original claims 1 and 2, as well as at page 11, lines 7-10. Claims 9-12 are amended only for formalities, such as claim dependencies. Applicants have added claims 20-25 which depend from claim 16, solely to replace the canceled claims 3-8. Claims 20-25 are essentially identical to original claims 3-8, except for a few formality changes (such as changes in claim dependencies). The amendments and new claims are made solely to expedite prosecution of the application, and Applicants reserve the right to prosecute claims of similar or differing scope in subsequent applications. No new matter is being introduced.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Claim rejections under 35 U.S.C. 112, second paragraph

Claims 2-9, 11 and 17-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. To expedite prosecution, Applicants have amended the claims to incorporate the Examiner's suggestions. Such amendments are not made in acquiescence of the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope.

Specifically, the Office Action objects to the recitation "in the region of VEGF beginning at nucleotide 259 and ending at nucleotide 293" in claim 16. Claim 16 has been amended

without such recitation, thus rendering the rejection moot. Further, the Office Action objects to the recitation of "from among SEQ ID NOS:" in claims 2, 7, 17, and 19. Solely to expedite prosecution, Applicants have amended claim 2 by adding the Markush language, as suggested by the Examiner. Claims 7, 17, and 19 have been canceled without prejudice, thus rendering the rejection moot.

Accordingly, Applicants submit that all claims as amended comply with the requirement of 35 U.S.C. 112, second paragraph. Reconsideration and withdrawal of rejections under 35 U.S.C. 112, second paragraph, are respectfully requested.

Claim rejections under 35 U.S.C. 102(e)

Claims 2-3, 9, 11, and 16-19 are rejected under 35 U.S.C. 102(e) as allegedly being anticipated by Uchida et al. [US 6,150,092]. Specifically, the Office Action asserts that "[t]his rejection is applied as the invention is interpreted to read on antisense to a target region." Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

The standard for anticipating a claim is clearly outlined in MPEP 2131, and this standard is further supported by the Courts. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1978).

As described above, Applicants have amended claim 2 by using the Markush language as suggested by the Examiner. Claim 16 has also been amended without the recitation of "in the region of VEGF beginning at nucleotide 259 and ending at nucleotide 293." Each of the claims now refers to a set of specific antisense nucleic acids that are not disclosed in Uchida et al. Applicants submit that Uchida et al. do not disclose each and every element of the amended claims. Accordingly, reconsideration and withdrawal of rejections under 35 U.S.C. 102 are respectfully requested.

Claim rejections under 35 U.S.C. 103(a)

The Examiner has rejected claims 2-3, 9-12, and 16-19 as being allegedly obvious over Uchida et al. (U.S. 6,150,092) and Robinson et al. (5,814,620; 5,710,136; and 5,801,156), while claims 4-8 are allegedly obvious over Uchida et al. in view of Barleon et al. and Chan et al.

Specifically, the Office Action asserts that, "[t]he antisense oligonucleotides claimed by Uchida et al. are targeted, for example, to the specific region of VEGF nucleic acid SEQ ID NO: 7. All of the specifically recited antisense oligonucleotides of instant claims 2, 10, 12, 17 and 19, for example, are all targeted to SEQ ID NO:7 of Uchida et al., which region is relatively small at 42 nucleotides in length. Further, many of the recited antisense oligonucleotides of instant claims 2, 10, 12, 17 and 19 overlap, embrace, or are embraced by the specifically claimed antisense of Uchida et al. claim 7, for example (SEQ ID NOS: 51, 54, 53, 50, 49, 138, and 141 of Uchida et al., for example)." See Office Action, the paragraph bridging pages 5 and 6.

Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

Applicants submit that the pending claims as amended are drawn to specific oligonucleotides wherein these specific oligonucleotides are modified to comprise a plurality of phosphorothioate (PS) moieties. As described above, claims 2 and 16 have been amended, thereby overcoming the novelty rejection.

Applicants maintain, for the reasons already made of record as well as the reasons presented below, that the claimed oligonucleotides are not obvious in view of the cited art.

1. <u>The cited references fail to teach each and every limitation of the claimed invention.</u>

Although certain of Applicants' sequences fall within the region defined by Uchida's SEQ ID NO: 7, Uchida et al. do not disclose the exact nucleic acids recited in claim 2 (e.g., SEQ ID NOS: 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 21, 28 and 29). In addition, Uchida et al. do not disclose the modified form of these exact nucleic acids <u>which comprise a plurality of phosphorothioate moieties</u>, as recited in claim 2. Applicants submit that none of Robinson et al., Barleon et al., and Chan et al. can overcome the deficiencies of Uchida et al. Therefore, the proposed combination of these cited prior art references fails to teach each and every limitation of the claimed invention.

The Examiner may have relied on alleged knowledge in the art in order to modify the antisense nucleic acids of Uchida et al. in order to arrive at the presently claimed nucleic acids. However it is Applicant's position that one of ordinary skill in the art would not have, upon review of Uchida et al., been motivated to make any phosphorothioate modified antisense probes, and certainly not the presently claimed probes.

2. The cited references fail to provide sufficient motivation for a skilled artisan to develop the claimed invention.

MPEP 2142 sets forth criteria that must be met in order to establish a prima facie case of obviousness. These criteria include the requirement that there must be some motivation for one of ordinary skill in the art to modify the prior art reference to arrive at Applicants' invention.

It is Applicants' position that the Examiner has failed to make a prima facie case for obviousness because Uchida et al. do not provide any motivation for one of ordinary skill in the art to make the claimed phosphorothioate modified antisense probes. Moreover, the motivation cannot be found in any of the other cited references.

In order to arrive at the presently claimed invention, one of ordinary skill in the art would need to change the sequence of one of the antisense probes described in Uchida et al. and, further, introduce phosphorothioate modifications. Uchida et al. disclose unmodified antisense probes that are effective in decreasing VEGF expression in cell-free assays (see, e.g., Uchida et al., Tables 1-8). However, as noted in the Declaration under 37 CFR 1.132 from Dr. Gill (enclosed herewith in unexecuted form, to be submitted as a signed document shortly), phosphorothioate modifications are employed only when an antisense probe is intended for use in cells. Therefore, the unmodified probes described by Uchida et al. would not render obvious phosphorothioate modified probes unless there were some evidence that such modified probes would be effective in cells.

Although Uchida et al. briefly describe cell-based assays with PS-modified forms of antisense probes, these PS-modified probed did not work well in cells. For example, Table 9 of Uchida et al. clearly shows that the amount of VEGF expression in the presence of the PS-modified probes remained high, ranging from 54% to 70% of normal (59% to 82% when corrected for the baseline inhibition seen in the controls).

The ineffectiveness of the probes described in Uchida et al. to affect VEGF expression in cells is further substantiated by the Declaration from Dr. Gill, noting that the cell-based assays were performed at an exceptionally high concentration of phosphorothioate modified probe. While the cell-free assays were performed with 0.4 micromolar concentrations of antisense nucleic acids, the cell-based assays were performed at a 50-fold higher concentration of 20 micromolar. According to Dr. Gill, the concentration of 20 micromolar is so high as to create non-specific results in many instances. And yet, despite the high concentration, none of the six phosphorothioate modified probes tested by Uchida et al. had a strong effect on VEGF expression in cells.

Furthermore, unmodified probes that were highly effective for inhibiting VEGF expression in the cell-free assay were, after phosphorothioate modification, poorly effective in the cell-based assays. As noted by Dr. Gill, the A311 probe (SEQ ID NO:51 in Uchida et al.) inhibited 96% of VEGF expression in the cell-free assay, but only inhibited 22% to 28% of VEGF expression in cells (and at a 50-fold higher concentration). Dr. Gill concludes from this discrepancy that the cell-free assay performed by Uchida et al. is a poor predictor of phosphorothioate modified probes that will be effective in cells.

Accordingly, one of ordinary skill in the art would not have been motivated to generate phosphorothioate modified variants of the probes described in Uchida et al. Having seen from Uchida et al. that six out of six probes identified through the cell-free assay were poorly effective in the cell based assay, one of ordinary skill in the art would not be motivated to adjust the disclosed probe or modify them for use in cells.

To conclude, one of ordinary skill in the art would appreciate that Uchida et al. provides no meaningful guidance for the selection of antisense probes for use in cells. Even if one accepts the predictions regarding regions in the in vitro assays (which there is substantial reason to doubt), it does not appear that these predictions transfer to the cellular setting or to phosphorothioate modified probes. Therefore, one of skill in the art would not be able to discern any particular variant sequences to be made on the basis of Uchida et al. and to further modify these variant sequences with phosphorothioate. Given that none of SEQ ID NOS: 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 21, 28 and 29 are disclosed literally in Uchida et al., it is unreasonable to assume that one of ordinary skill in the art could find in the teachings of Uchida et al. any motivation to make those particular sequences and to further modify these oligonucleotides with

phosphorothioate. In addition, no other reference cited provides any sequence that is identical or similar to those of SEQ ID NOS: 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 21, 28 and 29, let alone the PS-modified forms of these oligonucleotides.

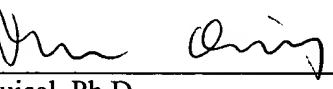
Accordingly, Applicants submit that all of the pending claims are non-obvious in view of Uchida et al. Furthermore, since none of the defects of Uchida et al. are cured by the other cited references, Applicants assert that the claims are not obvious in view of all cited references. Applicants respectfully request reconsideration and withdrawal of the rejection of the pending claims under 35 USC § 103.

CONCLUSION

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims are now in condition for allowance and early notification to this effect is earnestly solicited. Any questions arising from this submission may be directed to the undersigned at (617) 951-7000.

If there are any other fees due in connection with the filing of this submission, please charge the fees to our **Deposit Account No. 18-1945.** If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit account.

Respectfully Submitted,



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